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**NATIONAL STANDARD OF THE PEOPLE'S REPUBLIC
OF CHINA**

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GB/T 21415-2008/ISO 17511: 2003

**In vitro diagnostic medical devices - Measurement of
quantities in biological samples - Metrological
traceability of values assigned to calibrators and
control materials**

体外诊断医疗器械 生物样品中量的测量

校准品和控制物质赋值的计量学溯源性

(ISO 17511: 2003, IDT)

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Foreword

This Standard is identical to ISO 17511: 2003 *In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials*.

In order to ease of use, following editorial changes of this Standard are as follows:

- Modified the “international standard” to “the Standard”;
- Replaced the comma “,” with a decimal point “.”;
- Deleted the foreword of international standards;

The Standard was proposed by China Food and Drug Administration.

The Standard is under the jurisdiction of National Technical Committee (SAC/TC 136) on System of Medical Clinical Test Lab and in Vitro Diagnostic System of Standardization Administration of China.

The responsible drafting organizations of this Standard are Beijing Institute of Medical Device Testing and Roche Diagnostics (Shanghai) Co., Ltd.

The chief drafting staff of this Standard of this part includes Zong Yulong, Feng Renfeng, Zhang Xinmei, Hu Dongmei, Tao Yuan and Kang Juan.

Introduction

For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and that the results reported to the physicians or other health care personnel and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space.

NOTE In this Standard the concept "accuracy of measurement" (see 3.1) is related to both "trueness of measurement" (see 3.33) and "precision of measurement" (see 3.23) whereas the Directive 98/79/EC on in vitro diagnostic medical devices uses the term "accuracy" instead of "trueness".

To allow 'correct medical interpretation' involves more than the metrological (analytical) aspects of the traceability chain. As the measurement results are eventually used by the physician for the benefit of the patients, the physician should gather information on a number of other aspects, such as knowledge about the pre- and post- analytical phase, the diagnostic sensitivity and specificity, and relevant reference interval(s). The present Standard deals only with the analytical aspects of measurements in Laboratory Medicine (see also 1 e)).

The measurement of quantities in biological samples requires reference measurement systems including:

- the definition of the analyte in the biological sample with regard to the intended clinical use of the measurement results;
- a reference measurement procedure for the selected quantity in human samples;
- suitable reference materials for the selected quantity, e.g. primary calibrators and secondary matrix-based calibrators that are commutable.

The trueness of measurement of a value assigned to a defined quantity of a calibrator or trueness control material, depends on the metrological traceability of the value through an unbroken chain of alternating measurement procedures and measurement standards (calibrators), usually having successively decreasing uncertainties of measurement (see Figure 1). The uncertainty of the value assigned to a given calibrator or trueness control

material depends on the stated metrological traceability chain and the combined uncertainties of its links.

The ideal end-point of a metrological traceability chain is the definition of the relevant unit of the International System of Units (SI), but the selection of steps and the level at which metrological traceability for a given value stops, depend on the availability of higher order measurement procedures and calibrators. In many cases, at present, there is no metrological traceability above the manufacturer's selected measurement procedure or the manufacturer's working calibrator. In such cases, trueness is referred to that level of the calibration hierarchy until an internationally agreed reference measurement procedure and/or calibrator becomes available.

The objective of a chosen metrologically traceable calibration is to transfer the degree of trueness of a reference material, and/or reference measurement procedure, to a procedure that is of a lower metrological order, e.g. a routine procedure. Metrological traceability of calibration requires that the reference and routine measurement procedures measure the same measurable quantity with an analyte of the same pertinent characteristics.

In this context, it is important to recognize that different procedures purporting to measure the same quantity may in fact give different results when applied to a particular sample or reference material. This may arise, for example, when two or more immunoprocures purporting to measure the concentration of a hormone such as thyrotropin (thyroid stimulating hormone, TSH) are applied to a reference material of the hormone, because the respective reagents recognize and react to different extents with various epitopes in the material, thus leading to results for different although related quantities.

Laboratory medicine routinely provides results for 400 to 700 types of quantity. For most of these, the metrological traceability of the assigned value for a product calibrator stops after only one metrologically higher step consisting of a (reference) measurement procedure, or after two steps consisting of a measurement procedure and a (reference) calibrator. The reason is that many of such quantities are related to mixtures of molecular

species with clinically relevant properties in common, but with different structures and molecular masses in varying proportions, e.g. glycoproteins.

Depending on the possibility of metrological traceability to SI and on the availability of various metrological levels of measurement procedures and calibrators, the following five typical upper ends of the metrological traceability chain can be identified.

a) Quantities for which results of measurements are metrologically traceable to SI.

A primary reference measurement procedure and one or more (certified) primary reference materials (used as calibrators) are available. These levels exist for approximately 25 to 30 types of quantity having well defined components, e.g. some electrolytes, metabolites, steroid hormones, and some thyroid hormones. These types of quantity cover a large proportion of the routine results provided by medical laboratories (see 4.2.2, 5.2, Figures 1 and 2).

b) Quantities for which results of measurements are not metrologically traceable to SI.

1) An international conventional reference measurement procedure (see 3.12) (which cannot be called a primary reference measurement procedure) and one or more international conventional calibration materials (see 3.11) with values assigned by that procedure are available. These conditions apply for quantities with components such as HbA1c (see 5.3 and Figure 3).

2) An international conventional reference measurement procedure is available but no international conventional calibration materials. These conditions apply for about 30 types of quantity with components such as haemostatic factors (see 5.4 and Figure 4).

3) One or more international conventional calibration materials (used as calibrators) with a protocol for value assignment are available, but no international conventional reference measurement procedure. These conditions apply for over 300 types of quantity, e.g., for quantities referred to World Health Organization's International Standards, such as protein hormones, some antibodies, and tumour markers (see 5.5 and Figure 5).

4) Neither reference measurement procedure nor reference materials for calibration

are available. The manufacturer can establish 'in-house' measurement procedure(s) and calibrator(s) to support value assignment to his product calibrator. These conditions apply for about 300 types of quantity with components such as tumour markers and antibodies (see 5.6 and Figure 6).

The principles of the respective transfer protocols (calibration hierarchies) are presented, given the provisions of GB/T 19702 and GB/T 19703 on the description of reference materials.

It is the aim of metrology in laboratory medicine to improve metrological traceability for results of a type of quantity from the conditions described under b2), b3), and b4) to those of b1) by providing the missing reference measurement procedures and reference materials, based on international consensus.

The special problems of metrological traceability for values of catalytic concentration of enzymes are considered in ISO 18153.

In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials

1 Scope

This Standard specifies how to assure the metrological traceability of values assigned to calibrators and control materials intended to establish or verify trueness of measurement. The calibrators and control materials are those provided by the manufacturers as part of, or to be used together with, in vitro diagnostic medical devices.

External quality assessment (survey) samples, with proven commutability, whose values have been assigned by means of internationally agreed reference measurement systems or internationally agreed conventional reference measurement systems fall within the scope of this Standard.

This Standard is not applicable to:

- a) control materials that do not have an assigned value and are used only for assessing the precision of a measurement procedure, either its repeatability or reproducibility (precision control materials);
- b) control materials intended for intralaboratory quality control purposes and supplied with intervals of suggested acceptable values, each interval obtained by interlaboratory consensus with respect to one specified measurement procedure, and with limiting values that are not metrologically traceable;
- c) correlation between results of two measurement procedures at the same metrological level, purporting to measure the same quantity, because such 'horizontal' correlation does not provide metrological traceability;
- d) calibration derived from correlation between the results of two measurement procedures at different metrological levels, but with quantities having analytes of different

characteristics;

e) metrological traceability of routine results to the product calibrator and their relations to any medical discrimination limit;

f) properties involving nominal scales, i.e. where no magnitude is involved (e.g. identification of blood cells).

2 Normative references

This Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text, and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies (including amendments).

GB/T 19702-2005 In vitro diagnostic medical devices—Measurement of quantities in samples of biological origin—Presentation of reference measurement procedures (ISO 15193:2002, IDT)

GB/T 19702-2005 In vitro diagnostic medical devices -- Measurement of quantities in samples of biological origin -- Description of reference materials (ISO 15194:2002, IDT)

International Vocabulary of Basic and General Terms in Metrology, 2nd edition, ISO, Geneva, 1993.^{1) 2)}

¹⁾ This monograph has been prepared simultaneously in English and French by a joint working group consisting of experts appointed by: BIPM (International Bureau of Weights and Measures), IEC (International Electrotechnical Commission), IFCC (International Federation of Clinical Chemistry and Laboratory Medicine), ISO (International Organization for Standardization), IUPAC (International Union of Pure and Applied Chemistry), IUPAP (International Union of Pure and Applied Physics), OIML (International Organization of Legal Metrology)

²⁾ The abbreviation VIM:1993 is used in this Standard [VIM:1993, 3.5]

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